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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/305,084	05/04/1999	Robert J. Schneider	5914-080-999	1583

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
08/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/305,084	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *43-45 and 56-76* is/are rejected.

7)☐ Claim(s) *45-55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 43, 45 have been amended. Claims 60-76 have been added. Claims 43-76 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-45, 56-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a patient having metastatic melanoma comprising the administration of antagonists of ETB which are peptides or antibodies, does not reasonably provide enablement for a method of treating a patient having metastatic melanoma comprising antagonizing the ETB receptor, or a method of "preventing" metastatic melanoma in a patient diagnosed with melanoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 43, 56, 60, 62 encompass the selective antagonization of the ETB receptor, which is broader in scope than the administration of ETB receptor antagonists. The specification states that the melanoma cascade can be blocked by both direct and indirect mechanisms and contemplates that the ETB antagonist may include agents which block the activation of a caspase such as caspase-8 (page 24, line 28 to page 25, line 4). The specification further contemplates that catenin proteolysis resulting from ET-1/ETB receptor engagement may also be specifically blocked. However, the specification fails to teach how catenin proteolysis resulting from ET-1/ETB receptor engagement can be the result of a selective antagonization of the ETB receptor versus the ETA receptor. Bagnato et al (Cells Tissues Organs, 2007, Vol. 185, pp. 85-94) teach that ET-1/ETA receptor engagement in ovarian carcinoma cells mediates the reduction of E-cadherin and the localization of Beta-catenin in the nucleus rather than at the cell surface (pages 88-90 under the heading "ET-1 Axis in Epithelial-Mesenchymal Transition"). Thus it appears that ET-1 results in down regulation of E-cadherin and loss of functional beta-catenin

when either of the ETA or ETB receptors are engaged. The instant specification fails to teach how specific ETB antagonists which are interfering in the downstream effects of the ETB receptor can be specific for ETB in light of the overlap between the downstream effects of the ETA rector and the ETB receptor. Bagnato et al teach that engagement of ET-1 at the ETA receptor leads to PI3-K to ILK to GSK-3beta activation, which leads to down regulation of E-cadherin and loss of functional beta-catenin (Figure 1), which corroborates the teachings of the instant specification with regard to the effect of ET-1 on the ETB receptor. One of skill in the art would be subject to undue experimentation in order to provide a specific ETB receptor antagonist which blocks the activation of a caspase, blocks the activation of a catenin but which would not block the activation of the same said caspase or catenin resulting from ET-1/ETA receptor engagement because it appears that there is overlap in the downstream signaling of the ETA and the ETB receptors, and that both receptors result in down regulation of E-cadherin and loss of functional beta catenin when engaged by an ET-1 ligand. Thus, interference with the downstream signaling of the ET-1/ETB engagement by agents which inhibit said downstream signaling at proteins which were not ET-1 or ETB could not be attributed to a selective antagonization of the ETB receptor. Further, the specification fails to teach agents which can be administered to individuals having melanoma, wherein said agents would treat melanoma by inhibition of this intracellular signaling pathway through the ETB receptor. It is noted that antibodies bind proteins and can inhibit the action of a protein, but antibodies are not normally taken up into the cytoplasm of a cell unless said antibodies are targeted to an internalizing receptor. Thus the inhibition of a signaling cascade similar to the one set forth in Bagnato et al Figure 1 would not be amenable to the use of antibodies which bound to PI3-K, ILK or GSK-3Beta, because said antibodies would not contact the target proteins in the cytoplasm if administered to a patient with melanoma.

Claims 60-76 are drawn to the "prevention" of metastases in patients already diagnosed with malignant melanoma. When given the broadest reasonable interpretation, "prevention" reads on the complete absence of metastases in said individuals. It is noted that the specification teaches the inhibition of metastatic melanoma rather than the "cure" of metastatic melanoma. The state of the art with respect to the elimination of all cancer cells, or the absence of all metastatic cells is not well developed. One of skill in the art would readily accept that the

formation of metastases could be inhibited in an individual diagnosed with melanoma, but that it would not be reasonable to conclude that the instant invention would prevent metastatic melanoma in every individual diagnosed with melanoma. Amendment of claims 60 and 69 to recite a "method for inhibiting the development of metastatic melanoma in a patient having melanoma" rather than a "method for preventing metastatic melanoma in a patient diagnosed with melanoma" would overcome this particular ground of rejection.

Claims 43-45, 56-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 43-45, 56-62, 68, 69, 75 and 76 include a genus of direct and indirect ETB receptor antagonists, and thus include any small molecule inhibitor which can act as an antagonist of the ETB receptor by directly binding thereto, or which can antagonist the ETB receptor indirectly by interfering with the downstream signaling cascade associated with the ETB receptor. The specification suggests the inhibition of caspase-8 as a downstream antagonists of the ETB receptor. However the specification fails to describe any molecule which can inhibit caspase-8 activation through the ETB receptor, which would be differentiated from the inhibition of caspase-8 activation by any other means not connected to the ETB receptor. further, the description of the known specific ETB receptor antagonists which are all peptide in nature fails to adequately describe the small molecule inhibitors which can directly or indirectly antagonize the ETB receptor because the genus of small molecule inhibitors are not limited to peptides and therefore can encompass natural and synthetic organic compounds found in natural sources and in various libraries. Claims 43-45, 48, 56-62, 68-69, 75 and 76 encompass the administration of ETB receptor antagonists which are not limited to the known antagonists of BQ788, IRL-1038, RES-701-1. Claims 58, 59, 68, and 76 exemplify that the ETB receptor antagonists include new receptor antagonists which have been identified in an in vitro assay. The specification and the art at the time of filing teach specific ETB receptor antagonists which are peptides, although the specification contemplates that the ETB receptor antagonists include small molecule inhibitors

(page 25, line 14) which are beyond the scope of peptide inhibitors or antagonistic antibodies. The specification contemplates a wide genus of compounds which can function as a ETB antagonist. The specification provides as assay to identify putative antagonists of ETB based on modulation of E-cadherin expression in vitro. However, neither the specification nor the prior art identifies specific inhibitors of ETB which are not peptides. The specification does not provide a nexus between a chemical structure and an antagonistic effect on the ETB receptor. Thus, one of skill in the art would be required to first identify the ETB antagonists which are small, non-peptide molecules before carrying out the instant methods of treatment. Because that which has not yet been identified cannot be adequately described, one of skill in the art would reasonable conclude that applicant was not in possession of a genus of small molecule antagonists of ETB on which the instant method claims rely.

Claims 60 and 69 have been amended to recite the limitation “patient diagnosed with melanoma”. This limitation lacks support in the originally filed disclosure. Amendment of claims 60 and 69 to recite a "method for inhibiting the development of metastatic melanoma in a patient having melanoma” rather than a "method for preventing metastatic melanoma in a patient diagnosed with melanoma" would overcome this particular ground of rejection.

Claims 46-55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

All other rejections and objections as set forth or maintained in a prior office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643